REMARKS/ARGUMENTS

The presently outstanding non-final Office Action in the subject case, dated 01/24/2005, set a three month shortened statutory period for response, which expires **04/25/2005.**

In that Office Action, claims 1-22, pending in the application, were rejected, as follows:

1) Claims 1-22 were rejected under 35 USC § 112 as being indefinite.
2) Claims 1, 3, 6-8, 11-16 and 22 were rejected under 35 USC §102(e) as being anticipated by Thomas et al. 6,727,070.
3) Claims 2, 4, 5, 9, 10 and 17 were rejected under 35 USC §103(a) over Michnick et al. and Thomas.
4) Claims 18-21 were rejected under 35 USC §103(a) over Michnick, Thomas 2004/0241636 and Allen 2004/0198967.

Priority

The Office Action states that Applicant may wish to claim priority to 10/229,747 as a continuation-in-part application. It states that, presently, the priority date of the present application is its filing date, 11/6/2003.

Response

The Official Filing Receipt grants applicant the claimed priority to:

provisional applications 60/316,428, filed August 30, 2001,
provisional application 60/353,086, filed January 30, 2002,
full application 10/229,747 filed August 27, 2002 and

PCT application PCT/US02/27497 filed August 27, 2002.

Such priority is also claimed in the first paragraph of the present specification in accordance with MPEP 202.01, 37 CFR 1.78, and 35 USC §120. Both 10/229,747 and PCT/US02/27497 were pending as of the present filing date. In addition, priority under 35 USC §119 to PCT/US02/27497 was properly claimed in the original declaration filed in this case.

Therefore, Applicant respectfully disagrees with the statement in the Office Action that the present priority date is the filing date 11/6/2003.

The question becomes whether or not the present claims are supported in the priority applications. Support for granting the filing dates of the earlier applications is the following. In the first provisional application serial no. 60/316, 428, at page 8, it is stated:

> Cell lines may be modified by knocking out specific genes, introducing specific genes, e.g. the EA coding gene, enhancing or diminishing the expression of a protein or the like. The modification may be transient, as in the case of introduction of antisense DNA or dsRNA or may be permanent, by deleting a gene, **introducing a gene encoding the antisense mRNA of the target protein**, adding a dominant recessive gene, or the like. Research animals may be employed of various strains, where the strains are a result of naturally occurring mutations and breeding or using genetic modifications of embyronic or other cells with a resulting genetically modified host, which may be vertebrate, e.g. mammalian, fish, insect, or the like, or non-vertebrate, e.g. nematode, etc. Knock-out mice are extensively described in the literature. One may use the intact host, tissue from the intact host or cells from the intact host for the purposes of this invention. Illustrative of the development of knockout and knockin mice are Nozawa, et al., Transplantation 2001, 72:147-55; Ferreira, et al., Blood 2001 98:525-32; Kotani, et al., Biochem. J. 2001, 357:827-34; Zhou, et al., Int. J. Radiat. Biol. 2001, 77:763-72; and Chang, et al., Mol. Cell. Endocrinol. 2001, 180:39-46, and references cited therein, to provide only a few of the large number of publications concerning genetically modified mice. In addition one may use hybridomas, where a first cell having the desired gene(s) is fused with an immortalized cell under conditions where the chromosomes from the first cell are stably maintained. The gene(s) could be transcription factors, proteins of interest, e.g. human proteins in a non-human host cell, or provide for enhanced expression of a protein. (emphasis added)

The same language may be found on page 12, line 31, in application serial no. 10/229,747.

The specific language refers to dsRNA. RNAi is dsRNA. The Examiner is believed to make the erroneous distinction between inhibitory RNA that is specific for the fusion gene and inhibitory RNA that affects the expression of the fusion gene. Further, it is submitted that the language of the parent applications specifically provides for the event the Examiner distinguishes. Having inhibitory RNA for the target protein clearly includes within its scope, the fusion gene that has the target protein.

While the target protein may be other than the protein of the fusion protein, it may also be the same. In fact, in page 26, paragraph beginning on line 3 of 10/229,747 in recognition of this possibility, it is stated:

> The activity of the fusion protein may be determined by using host cells in which the expression of the natural protein does not occur, such as cells in which both copies of the natural protein have been knocked-out, **where antisense RNA is added to the host cell that inhibits the natural protein but not the fusion protein**, e.g. as to the non-coded 3'-region or includes the 5'-methionine codon, inhibits a transcription factor necessary for the natural protein, where the fusion protein has a different transcriptional regulatory region, if an enzyme, is shown to bind to its natural substrate and catalyze its reaction at a rate reasonably commensurate with the natural enzyme or, if not an enzyme, binds with an appropriate affinity to the proteins the natural protein binds to, etc." (emphasis added)

It is submitted that the Examiner errs in the denial of the parent filing dates and is respectfully requested to withdraw the denial.

Declaration

The declaration was objected to as having been altered.

Response

A new declaration, using currently approved USPTO FORM SB/01, accompanies this response. This declaration should obviate the Examiner's objection, although in fact the original declaration is not defective in that it was not altered after signing, and MPEP 605.04(a) suggests but does not require that the signing individual initial and date the alteration.

Rejection of Claims 1-22 were 35 USC § 112 as being indefinite.

A sincere effort has been made to avoid the rejections under 35 USC §112. Most of the objections are believed to have been avoided, applicant's attorney having made a sincere effort to respond to the Examiner's objections. However, it is applicant's attorney's position that the claims are directed to those skilled in the art, the claims serve to delimit what is to be considered an infringing act and that the claims are not explanatory of the process, but rather describe the monopoly that applicant claims.

As the Examiner appreciates, claiming the subject invention is difficult in that the invention encompasses a number of different pathways that the inhibiting nucleic acid may affect. The inhibiting nucleic acid may directly affect the expression of the fusion protein. In the absence of expression of the fusion protein, there will be no ED for formation of β-galactosidase. The nucleic acid may inhibit expression of a protein that complexes with the polypeptide and causes degradation of the fusion protein, resulting in the absence of the ED and no formation of β-galactosidase. The nucleic acid may inhibit the expression of a transcription factor, so that there is no expression of the fusion protein. The questions that can be asked with this system are manifold and can be used to evaluate pathways, evaluate potential drugs and evaluate the role of proteins in a cell. The claims have been written to encompass the various opportunities that the subject method provides.

How the various components of the method operate is not necessary to the claims. The claims provide for what is done and the outcome that is to be considered. The features of the claims are the use of an inhibiting nucleic acid, an expression construct expressing a fusion protein, EA and a substrate. In some cases there is a candidate compound present. Maintaining a cell comprising the expression construct of the fusion protein whereby the fusion protein may be expressed is clear. Providing EA to the fusion protein is a well known step in other assays that can be achieved by having EA expressed in the cell and employing a substrate that can be transported into the cell or using a cell lysate, where EA

is added to the lysate, along with a substrate. Observing a detectable product is the common outcome for using enzyme fragment complementation with β-galactosidase, so this is clear. The central feature is to use the fusion protein as the marker for determining the effect of the inhibiting nucleic acid on expression in the cell.

The rejection of claim 1 concerning "analyzing in a cell for the effect" is partially avoided and partially traversed. The claim is now directed to analyzing for the expression of the fusion protein, which should avoid the rejection. However, it is submitted that the claim does have the necessary steps for determining the "effect." The method leads to a determination of the effect or lack of effect on the expression of the fusion protein.

The rejection of claims 1 and 8 concerning the phrase "a fusion protein of the small enzyme donor fragment of β-galactosidase with a polypeptide" has been avoided by amendment, the language defining the fusion protein as the ED joined to the polypeptide.

The rejection of claims 1 and 8 concerning the phrase "affects the activity of β-galactosidase" has been avoided by amendment whereby the outcome is the effect on expression of the fusion protein.

The rejection of claims 1 and 8 concerning the phrase "providing said EA to any of said fusion protein produced in said cell" is respectfully traversed. There is no intention to suggest, nor does the language itself suggest that there is more than one fusion protein. The term "said" defines the specific fusion protein described previously and it is submitted that there is no ambiguity in the language.

The rejection of claims 1, 8 and 13 concerning the phrase "substrate produces a detectable product" has been avoided by amendment, the role of β-galactosidase being indicated.

The rejection of claims 6 and 15 concerning the phrase "said cell is grown in the presence of a candidate compound" is respectfully traversed. Those of skill in the art would know that one is interested in the effect of a compound on the cellular process that is established by the method. In addition, the specification makes clear what is intended. The Examiner's attention is respectfully directed to page 18, paragraph [00055].

The rejection of claim 18 for use of the word "system" is respectfully traversed. The term "system" has found ample acceptance in the patent office dealing with devices, electronic systems, business methods and numerous other situations. The Examiner is respectfully requested to do a quick search of claims including the term "system" to see how prevalent its use is. For example, see U.S. Patent nos. 6,432,720 and 6,856,778 as illustrative. Also, "system" is defined as "An assemblage of objects united by some form of regular interaction or interdependence; an organic or organized whole; as the solar system; a new telegraph system." Webster's New Collegiate Dictionary, G. & C. Merriam Co., Springfield, Mass., U.S.A., 1960, page 863.

Claim 18 is directed to a "system" of components that act together to be used in the claimed methods. Analogous to other fields of endeavor, the combination of components to perform various chemical or biological methods provide a system for performing these methods. In light of the fact that the term finds wide acceptance in the patent office and is clearly pertinent to the subject invention, it is submitted to be appropriate. So far as there being a rule that methods and products cannot be claimed together, this is directly contrary to product-by-process claims and is contrary to the directions in which the patent office has been going.

So far as the term "gene" in claim 18 referring to encoding the dsRNA, it is believed to be appropriate. As applicant's attorney understands the process, there are genes that encode RNA with repetitive sequences that form a hairpin that is subsequently processed to form the RNAi. As such, it is submitted that the language is appropriate.

All of the rejections under 35 USC §112 having been avoided and/or traversed, and there being no new matter, all of the language being inherent clarification or present in one or more original claims, the Examiner is respectfully requested to withdraw these rejections.

Rejection of Claims 1, 3, 6-8, 11-16 and 22 under 35 USC §102(e) as being anticipated by Thomas et al. 6,727,070.

The rejection of claims 1, 2, 6-8, 11-16 and 22 under 35 USC 102(e) based on Thomas ('070) is respectfully traversed. It is well established law that in rejecting the claims, the Examiner must consider every limitation in the claims. The present claims require that inhibiting nucleic acid, particularly RNA, species be used to determine the effect on expression of a protein. The effect on expression may be direct or indirect, in that the RNA species may interfere with the expression of the protein or may interfere with the expression of a different protein that modulates the expression of a protein of interest.

The term "expression" is well understood to mean the process whereby a gene is transcribed and translated to produce a protein, usually reflecting the codons present in the gene. Folding and solubility are different phenomena, although they may be related. Folding involves the nascent protein, possibly in conjunction with a chaperone, being organized to form the three-dimensional form of the protein. Solubility relates to the ability of the protein to remain in solution as a result of its solubility or the solubility of a complex that the protein forms with another compound. It is the essence of '070 that the compound must be formed in order for its solubility and/or folding to be determined. The inventors state, "There are three primary applications for the invention: screening of proteins for suitability in recombinant polypeptide production, screening for mutants or domain boundaries with altered folding and/or solubility profiles (e.g. , diagnosis of disease) and screening for drugs that modulate protein folding and/or solubility." Col. 35, lines 35 – 41)

Each of these purposes is directed to the physical structure of a protein, where the folding of the protein is the focus. Since folding has to do with the exiting of the nascent protein from the ribosome and its processing, particularly as associated with a chaperone, one is measuring this event or a subsequent modification of the protein that may result in loss of solubility. As the patentee states, the focus is the effect of the processing of the protein during and after expression on the protein's folding and solubility. The marker employed is the same ED as applicant use, but the patentee looks to see what the effect of the nature of the protein has on the activity of the ED in providing an active β-galactosidase. The modulation of the ED is associated with the effect of the folding on ED binding to EA or the removal of the ED by dissolution of the fusion protein.

The reference expresses the proteins in bacterial hosts, not very interesting for screening for drugs. The mammalian chaperones are not present and the only question being asked by the inventors is whether the expressed product is in the supernatant or in the pellet upon centrifugation. Furthermore, bacteria place misfolded proteins in inclusion bodies, as compared to eukaryotic cells that degrade the misfolded proteins. The clean separation observed by the patentee would be expected in bacterial cells.

Furthermore, if one obtains a negative result in the reference invention, it may be attributed to misfolding, precipitation, lack of expression, degradation or other event that inhibits binding of the ED to the EA. While one could perform an analysis for any precipitated protein, determining the reason for the absence of active ED is not possible where there is no protein. In the present invention one can carry out the experiment in the presence and the absence of the inhibiting nucleic acid. If there is no expression in the absence of the inhibiting nucleic acid, then one cannot use such a system. By contrast, in the reference, one cannot distinguish in eukaryotic cells whether a candidate compound has caused misfolding with degradation, inhibited expression or other event that prevents the ED from complexing with the EA. The present system asks a single question and receives a definite answer.

Why would anyone look at this reference and be led to use the mechanical aspects for a totally different purpose? There is nothing in the reference that suggests that the well-known marker fragment of β-galactosidase would serve for a purpose other than solubility or folding. Only solubility differences are exemplified, there is no showing that folding would also provide a distinction. The physical removal from solution is a simple physical phenomenon well known to make a substance unavailable for interactions with a substance in solution.

In addition, there is no showing that the fusion proteins would be stable in a mammalian cell or provide information on the degradative instability of the target protein or the interference with a pathway that provides for expression or non-expression of a protein of interest. After all, in the subject invention one is interested in learning whether an RNA molecule can modulate the expression of a protein of interest. If the fusion protein is unstable, then the method would not suffice. It is only when the fusion protein has substantial stability in the cell that the assay becomes of use and this can be readily determined by performing a control in the absence of the RNA expression inhibitor. In the subject invention the concern is whether one can detect the presence of the protein of interest as the fusion protein, not whether the fusion protein is soluble or insoluble.

The reference is in direct contrast to the subject invention where the essence of the invention is to determine the effect of interest on the formation of the protein. There is nothing in the subject application about whether the protein is functional or not as may be related to folding and solubility. One is solely concerned with the effect on expression. Rather than determining how a fusion protein is processed during its expression and subsequent existence in a cell, the subject invention is concerned about how an inhibiting nucleic acid affects the occurrence of the expression event, not the subsequent event during the process of expression and thereafter.

The reference and the subject invention employ similar agents for detection of the different phenomena of interest. It is not obvious to appreciate that one system may be

used in an entirely different way to measure entirely different phenomena. One might as well equate the use of heat to melt ice and cook food to kill infectious agents. Observing the melting of ice does not suggest that the heat could be used in a distinctively different way. Solving the problem of removing ice does not suggest that one could reduce disease by cooking food. One must conceive of the question to be asked and then conceive of how one can answer the question.

The present rejection avoids the issue, by comparing the agents that are employed in the two processes and totally ignores the different readouts and the different phenomena involved in the methods. For all of the above reasons, the Examiner is respectfully requested to withdraw this rejection.

Rejection of Claims 2, 4, 5, 9, 10 and 17 under 35 USC §103(a) over Michnick et al. and Thomas.

The next rejection is based on 35 USC §103(a) of claims 2, 4, 5, 9, 10 and 17 based on Michnick ('636) and Thomas ('070). Applicant need not go into the merits of the '636 reference, as the reference only has a priority date of May 30, 2003. Applicant's earliest parent has an effective date of August 30, 2001 and even the nonprovisional application 10/229,767 has the filing date of August 27, 2002. In both cases, the dates are earlier than the reference. The Examiner is respectfully requested to withdraw this rejection.

Rejection of Claims 18-21 under 35 USC §103(a) over Michnick, Thomas 2004/0241636 and Allen 2004/0198967.

The rejection of claims 18-21 is based on the above references to which is added Allen (US 2004/0198967). Allen suffers from the same deficiency as '636 and is not appropriately applied in the rejection as having an effective date subsequent to the effective

date of the subject application. The Examiner is respectfully requested to withdraw this rejection.

All of the rejections having been avoided and/or traversed, the Examiner is respectfully requested to withdraw the rejections and pass this application to issue.

Conclusion

Applicant request that this amendment to the claims and specification be entered and the rejections of claims 1-22 be withdrawn for the reasons advanced above. It is believed that the present Amendment is fully responsive to the presently outstanding Office Action and should place the application in condition for allowance. The allowance of currently pending claims 1-22, as well as the timely issuance of a Notice of Allowance is earnestly solicited. If a telephone conference would be useful in this case, the Examiner is respectfully requested to call the undersigned at the number below to discuss any prosecution issues.

Respectfully submitted,

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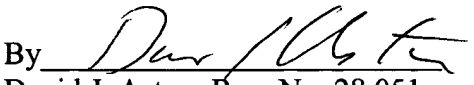
By 
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